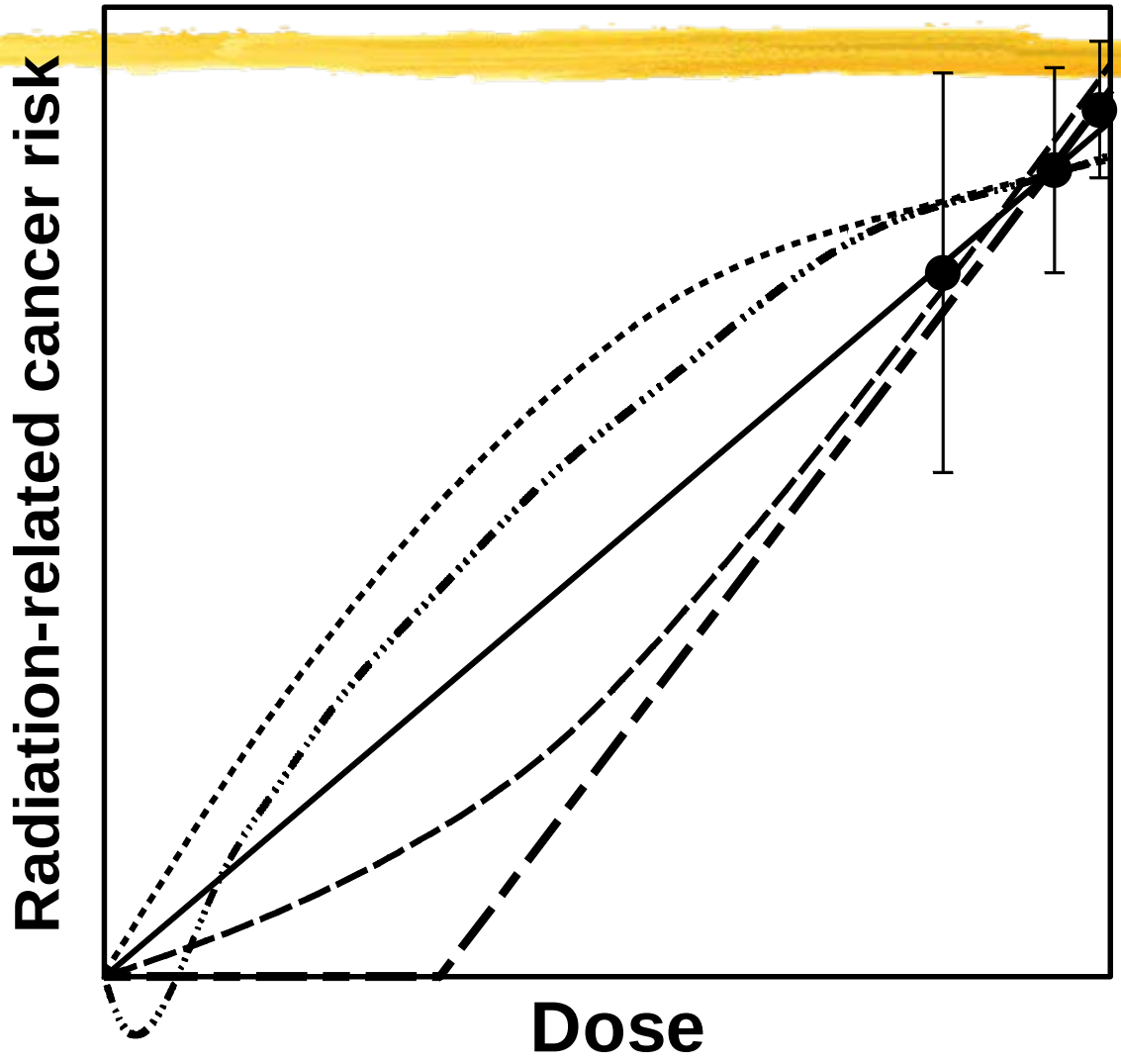
État actuel de nos recherches - réflexion sur les priorités de recherche en matière de radioprotection.

Elisabeth Cardis
Chef, Groupe Rayonnements
Centre International de Recherche sur le Cancer,
Lyon, France

Radiation Protection – *Today*

- Bases of radiation protection
  - Estimates of radiation induced cancer risk from:
    - atomic bomb survivors
    - patients irradiated for therapeutic purposes
    - populations with occupational exposures (miners)
    - animal experiments
    - mechanistic studies
  - Extrapolation models:
    - high doses to low doses
    - high dose rates to low dose-rates
    - over time, across countries, ...

Possible extrapolations of radiation-induced cancer risk to low doses



Outstanding questions in radiation protection

- Carcinogenic effects of low doses of radiation as a function of
  - Exposure pattern,
  - Radiation type,
  - Factors that may modify radiation risks
    - age at exposure, sex
    - genetic differences
    - other host and environmental effect modifiers
- Effects on risk of other diseases
  - Cardiovascular

Epidemiology – what is needed

- Targeted studies of populations with specific exposures of concern
  - Low dose, low dose-rate protracted or fractionated exposures
  - Particular radionuclides
  - Exposures in childhood and adolescence
  - Possible modifying factors of interest

Direct epidemiological evidence
- Requirements -

- Study population
  - Very large
  - Well-defined
  - No selection bias
- Follow-up / Case & control ascertainment
  - Complete, non-differential
  - Accurate diagnosis
- Dose-estimates
  - Individual
  - Accurate and precise
  - Quantify uncertainty and take into account in risk estimation process

Études épidemiologiques financées dans les 4ème et 5ème PCRD

- Envergure et financements plus limités que maintenant
- « Instruments de financement »
  - Actions concertées
  - Projets de recherche

... Exemples des leçons que nous en avons tirées

15-Country study of cancer risk among radiation workers in the nuclear industry LOWDOSERISK

- ***Objective***
  - direct estimation of the effect of low dose, protracted exposures to external-photon radiation
- ***Approach***
  - International Collaborative study
  - Retrospective cohort study
  - Much effort to assess and ensure comparability
    - Common core protocol
    - Studies of errors in doses

IRE, Japan

Commission canadienne de sûreté nucléaire
Canadian Nuclear Safety Commission

Nuclear industry workers

- *Characteristics*
  - Very large, stable populations
  - Well characterized exposures
    - Generally low doses, protracted
    - Mainly external γ–radiation
  - Detailed individual annual dose estimates - *measured in real time with personal dosimeters –*

... Relevant population for radiation protection

bmj.com

Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries

E Cardis, M Vrijheid, M Blettner, E Gilbert, M Hakama, C Hill, G Howe, J Kaldor, C R Muirhead, M Schubauer-Berigan, T Yoshimura, F Bermann, G Cowper, J Fix, C Hacker, B Heinmiller, M Marshall, I Thierry-Chef, D Utterback, Y-O Ahn, E Amoros, P Ashmore, A Auvinen, J-M Bae, J Bernar Solano, A Biau, E Combalot, P Deboodt, A Diez Sacristan, M Eklof, H Engels, G Engholm, G Gulis, R Habib, K Holan, H Hyvonen, A Kerekes, J Kurtinaitis, H Malker, M Martuzzi, A Mastauskas, A Monnet, M Moser, M S Pearce, D B Richardson, F Rodriguez-Artalejo, A Rogel, H Tardy, M Telle-Lamberton, I Turai, M Usel and K Veress

BMJ 2005;331;77-; originally published online 29 Jun 2005;
doi:10.1136/bmj.38499.599861.E0

- Largest analytical study of effects of low dose protracted exposures to date
- Most precise, direct estimates
- Estimates are statistically consistent with extrapolations from A-bomb data
- Confounding by smoking cannot be ruled out but unlikely to explain all increase

... Results suggest that at a small cancer risk exists, even at low doses typical of workers in this study

Case-control study of thyroid cancer in young people after the Chernobyl accident

- *Objectives*
  - To study the relation between radiation dose to the thyroid and risk of thyroid cancer
  - To study the roles of modifying factors in radiation induced thyroid cancer
- *Design*
  - Population based case-control study
  - Gomel and Mogilev regions in Belarus and Bryansk, Kaluga, Oriol and Tula regions in Russia
  - Children (<15) at the time of the accident
  - Study period: 1992-1998
  - 276 cases and 1300 controls

Risk of Thyroid Cancer After Exposure to ^{131}I in Childhood

Elisabeth Cardis, Ausrele Kesminiene, Victor Ivanov, Irina Malakhova, Yoshisada Shibata, Valeryi Khrouch, Vladimir Drozdovitch, Evaldas Maceika, Irina Zvonova, Oleg Vlassov, André Bouville, Guennadi Goulko, Masaharu Hoshi, Alexander Abrosimov, Jadvyga Anoshko, Larisa Astakhova, Sergey Chekin, Evgenyi Demidchik, Rosaria Galanti, Masahiro Ito, Elena Korobova, Evgenyi Lushnikov, Marat Maksioutov, Vladimir Masyakin, Alexander Nerovnia, Vladimir Parshin, Evgenyi Parshkov, Nikolay Piliptsevich, Aldo Pinchera, Semyon Polyakov, Nina Shabeka, Eero Suonio, Vanessa Tenet, Anatoli Tsyb, Shunichi Yamashita, Dillwyn Williams

Background: **After the Chernobyl nuclear power plant accident in April 1986, a large increase in the incidence of childhood thyroid cancer was reported in contaminated areas. Most of the radiation exposure to the thyroid was from iodine isotopes, especially ^{131}I. We carried out a population-based case–control study of thyroid cancer in Belarus and the Russian Federation to evaluate the risk of thyroid cancer after exposure to radioactive iodine in childhood and to investigate environmental and host factors that may modify this risk.** ***Methods:*** **We studied 276 case patients with thyroid cancer through 1998 and 1300 matched control subjects, all aged younger than 15 years at the time of the accident. Individual doses were estimated for each subject based on their whereabouts and dietary habits at the time of the accident and in following days, weeks, and years; their likely stable iodine status at the time of the accident was also evaluated. Data were analyzed by conditional logistic regression using several different models. All statistical tests were two-sided.** ***Results:*** **A strong dose–response relationship was observed between radiation dose to the thyroid received in childhood and thyroid cancer risk ($P<.001$). For a dose of 1 Gy, the estimated odds ratio of thyroid cancer varied from 5.5 (95% confidence interval [CI] = 3.1 to 9.5) to 8.4 (95% CI = 4.1 to 17.3), depending on the risk model. A linear dose–response relationship was observed up to 1.5–2 Gy. The risk of radiation-related thyroid cancer was three times higher in iodine-deficient areas (relative risk [RR]= 3.2, 95% CI = 1.9 to 5.5) than elsewhere. Administration of potassium iodide as a dietary supplement reduced this risk of radiation-related thyroid cancer by a factor of 3 (RR = 0.34, 95% CI = 0.1 to 0.9, for consumption of potassium iodide versus no consumption).** ***Conclusion:*** **Exposure to ^{131}I in childhood is associated with an increased risk of thyroid cancer. Both iodine deficiency and iodine supplementation appear to modify this risk. These results have important public health implications: stable iodine supplementation in iodine-deficient populations may substantially reduce the risk of thyroid cancer related to radioactive iodines in case of exposure to radioactive iodines in childhood that may occur after radiation accidents or during medical diagnostic and therapeutic procedures.** **[J Natl Cancer Inst 2005;97:724–32]**

Until the Chernobyl accident, the carcinogenic effect of exposure to ^{131}I was considered to be small compared with that of external photon exposure *(1,2)*. In fact, little information about the effects of exposure of the child's thyroid to radioactive iodine isotopes was then available, because most studies on the risk of cancer associated with exposure to ^{131}I had been conducted in adult populations with underlying thyroid disease. It was, however, well known that the child's thyroid was sensitive to external x-rays *(3,4)*.

Affiliations of authors: International Agency for Research on Cancer, Lyon, France (EC, AK, VD, VT); Medical Radiological Research Center RAMS, Obninsk, the Russian Federation (VI, OV, AA, SC, EL, MM, VP, EP, AT); Belarusian Center for Medical Technologies, Computer Systems, Administration and Management of Health, Minsk, Belarus (IM, SP, NS); Nagasaki University, Nagasaki, Japan (YS, SY); State Research Center—Institute of Biophysics, Moscow, the Russian Federation (VK); Institute of Physics, Vilnius, Lithuania (EM); Research Institute of Radiation Hygiene, St. Petersburg, the Russian Federation (IZ); National Cancer Institute, Bethesda, MD (AB); Clinic and Policlinic for Nuclear Medicine, Bayerische Julius-Maximilians University of Würzburg, Germany (GG); Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan (MH); Institute of Geological Sciences of the National Academy of Sciences of Belarus, Minsk, Belarus (JA); Center of Laser Medicine, Childhood Polyclinic No. 8, Minsk, Belarus (LA); Belarusian State Medical University, Minsk, Belarus (ED); Centre for Tobacco Prevention, Stockholm Centre of Public Health and Clinical Epidemiology Unit, Karolinska University Hospital, Sweden (RG); National Nagasaki Medical Center, Nagasaki, Japan (MI); Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, Moscow, the Russian Federation (EK); Republican Research Centre of Radiation Medicine and Human Ecology, Gomel, Belarus (VM); Belarusian State Medical University, Minsk, Belarus (AN, NP); Department of Endocrinology and Metabolism, University of Pisa, Italy (AP); Clinic of Oncology, Turku University Hospital, Turku, Finland (ES); Strangeways Research Laboratory, Cambridge, U.K. (DW).

Correspondence to: E. Cardis, PhD, International Agency for Research on Cancer, Lyon, France (e-mail: cardis@iarc.fr).

See "Notes" following "References."

DOI: 10.1093/jnci/dji129

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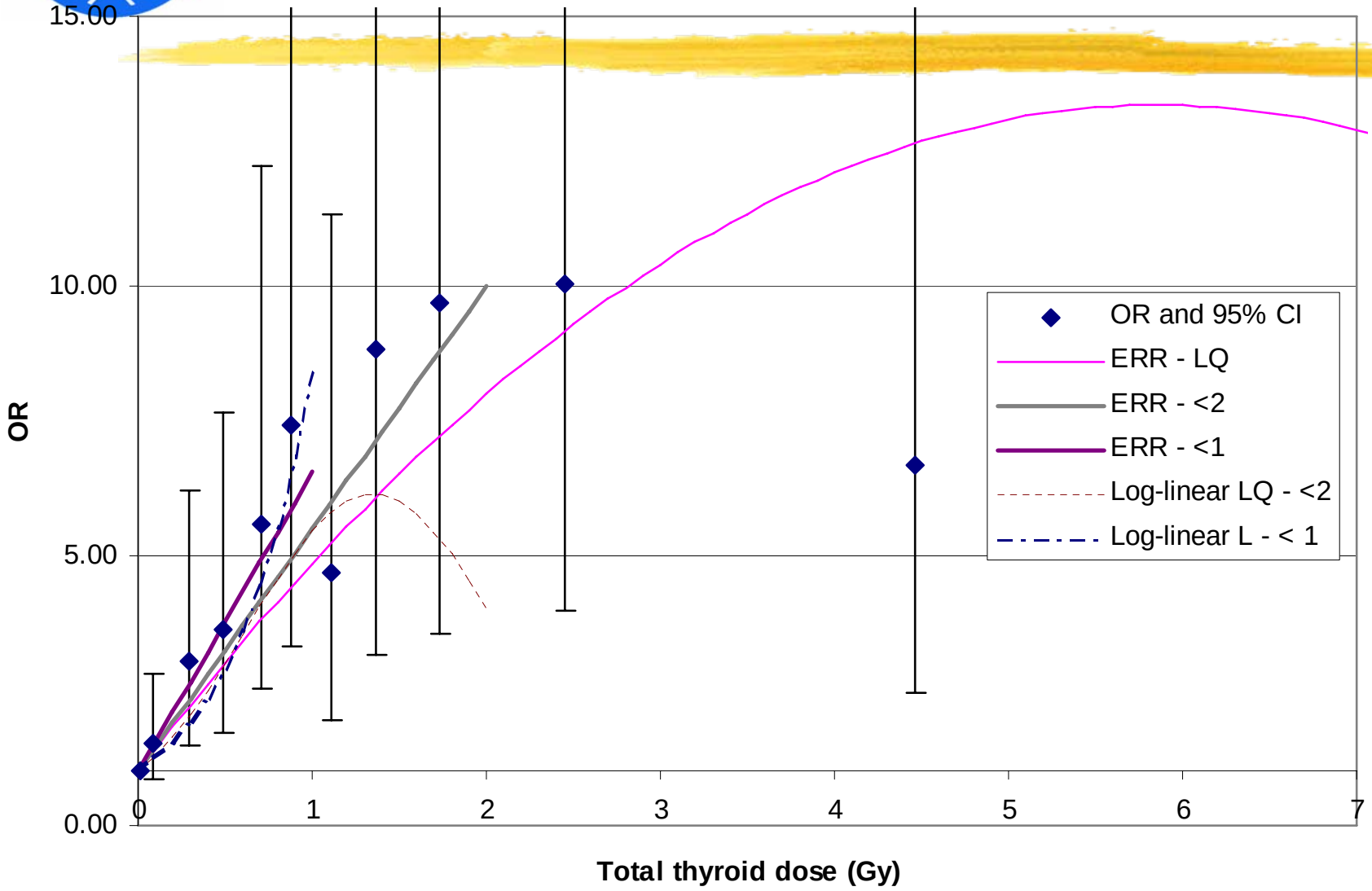
Summary of dose-response relationship



Analyses of modifying effect of stable iodine status

- **Iodine deficiency**

  OR at 1 Gy: 3.2 (95% CI = 1.9 to 5.5) times greater than in other areas

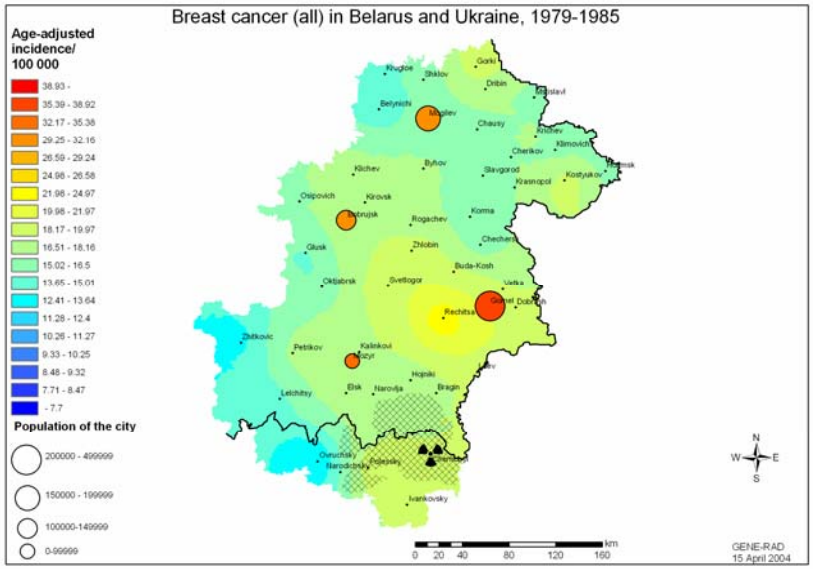
- **Stable iodine supplementation**

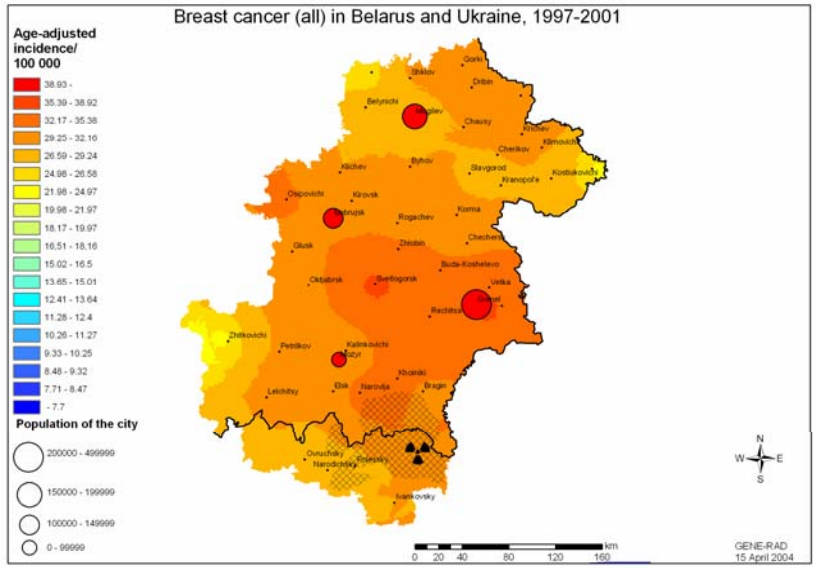
  OR at 1 Gy: 0.34 (95% CI = 0.1 to 0.9) lower than in subjects without

Breast cancer after Chernobyl GENE-RAD Interactions

- *Objectives*
  - To determine whether increase in pre-menopausal breast cancer incidence in Belarus and Ukraine is related to radiation exposure
  - To study possible interaction between radiation exposure and genes known to influence radiation sensitivity and risk of breast cancer
- *Approach – phase I*
  - Descriptive epidemiological study of breast cancer in contaminated areas of Belarus and Ukraine
  - Assessment of the feasibility and setting up of mechanisms and procedures for population based case-control study
  - Development and testing of dose reconstruction method

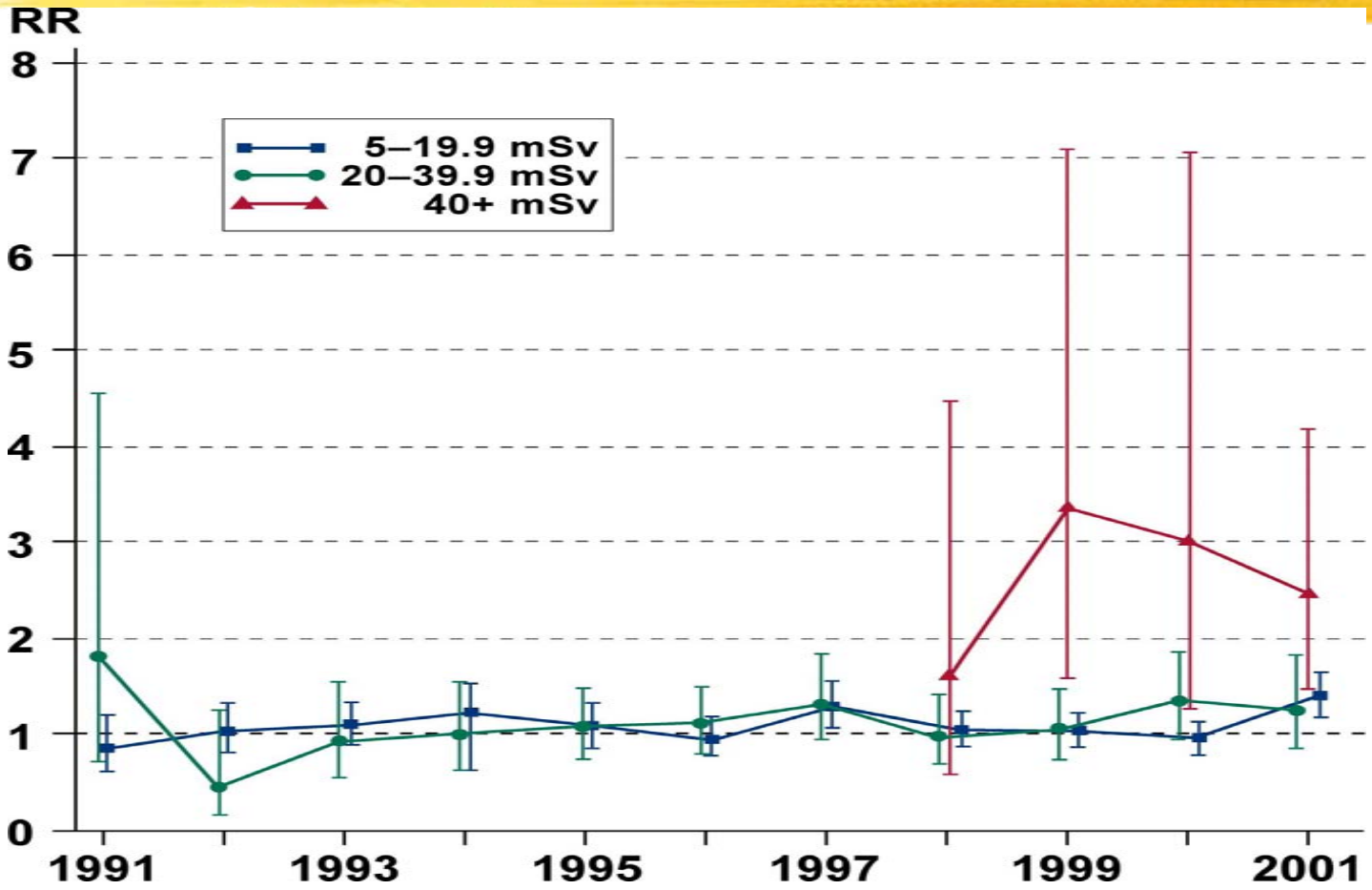
Breast cancer in young women after Chernobyl





Pukkala E, Kesminiene K, Poliakov S, Ryzhov A, Drozdovich V, Kovgan L, Kyyrönen P, Malakhova I, Gulak L and Cardis E. Breast cancer in Belarus and Ukraine after the Chernobyl accident. Int J Cancer www3.interscience.wiley.com, doi: 10.1002/ijc.21885 [epub ahead of print] 2006

Breast cancer in young women after Chernobyl



6ème PCRD - épidémiologie

- Instruments différents
  - Envergure et financements beaucoup plus conséquents
  - Gestion beaucoup plus lourde et responsabilité collective
  - Plus grande flexibilité
- Specific Targeted Research or Integration Project –
  - **Alpha-Risk** - Quantification des risques associés à des expositions faibles et étalées dans le temps (contamination interne alpha) *(coordinateur: IRSN – Margot Tirmarche)*
  - **Gene-Rad-Risk** – Interactions gènes-rayonnement dans l'étiologie du cancer du sein *(coordinateur: CIRC – E Cardis)*
  - **RACE** – Risque de maladies cardiovasculaires lié à la radiothérapie pour le cancer du sein
- Integrated Project –
  - **SOUL** – expositions dans l'Ural (Mayak, Rivière Techa, ...)

GENE-RAD-RISK Project (FP6)

- Objective
  - To examine the joint roles of radiation exposure and genetic susceptibility in the etiology of breast cancer in young women.
- Approach
  - Multinational nested case-control studies of breast cancer, nested in complementary cohorts:
    - cohorts of patients who survived a first cancer diagnosed before the age of 35;
    - cohorts of subjects with a known or suspected genetic predisposition to breast cancer – BRCA1 and 2 mutation carriers
- Genes of particular interest
  - BRCA1, BRCA2, ATM, NBS1, CHEK2, XRCC1, XRCC3, p53 and RAD50
  - involved in the detection and the repair of DNA damage produced by radiation
- Consortium
  - 12 partners, 8 countries

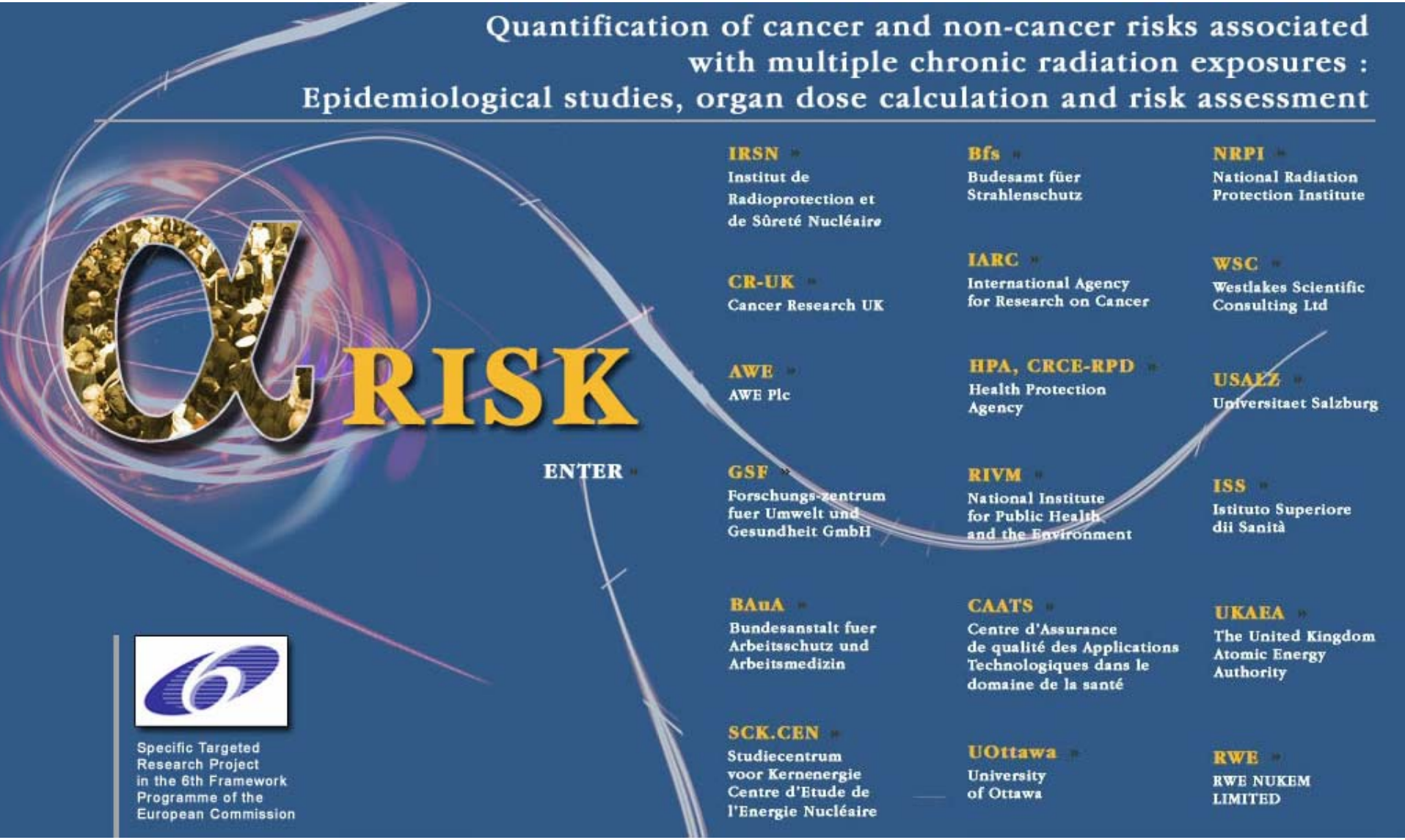
Cancer survivor cohorts

Name of study center(s)	Definition of study population	Age at exposure / first cancer	Approximate size of study population	Period for retrospective case ascertainment	Expected number of cases
Hodgkin's disease cohorts					
Netherlands Cancer Institute	Women HD patients from 4 hospitals treated in 1965-1988 who survived 5+ years	15-40	1500	1966-	110
Institute for Cancer Research, UK	Women HD patients treated with Rx in 1971-2004 who survived 5+ years	<35	2500-5000	1976-	150-200
South West Wales Cancer Institute	Women HD patients	<35	300	1962-	25
EORTC Lymphoma Group	Women with HD enrolled in EORTC, H89 trials	<39	2000	1964-98	25
Childhood cancer cohorts					
Institut Gustave Roussy	Childhood cancer survivors – 1945-1985 – France	0-16	3500	1993-	30
Istituto G. Gaslini – Piedmont chidhood cancer registry	Children treated in Genova/Monza	0-15	4 990	1993-	18
Netherlands Cancer Institute	Childhood cancer survivors	0-15	2-3000	1980-2004	20
Nordic Childhood Cancer Study	All Nordic cancer cases , 1960-1987	<20	25 000	1960-1991	24
UK Childhood Cancer Survivor cohort	All UK, 1940-1991; 5 year surv.	<15	18 000	1945-1999	40

BRCA1/2 carrier cohorts - expected number of cases

Name of study centre(s)	Incident cases	Retrospective cases	Total expected number of cases
France – Centre René Huguenin	25-46	84	109-131
Netherlands – Netherlands Cancer Institute	100-150	100	200-250
UK – University of Cambridge	49-81	147	196-228

- 500-650 cases expected
- Preliminary results in BRCA1/2 carriers show elevated RR for diagnostic exposures Andrieu et al, 2006.



http://www.alpha-risk.org

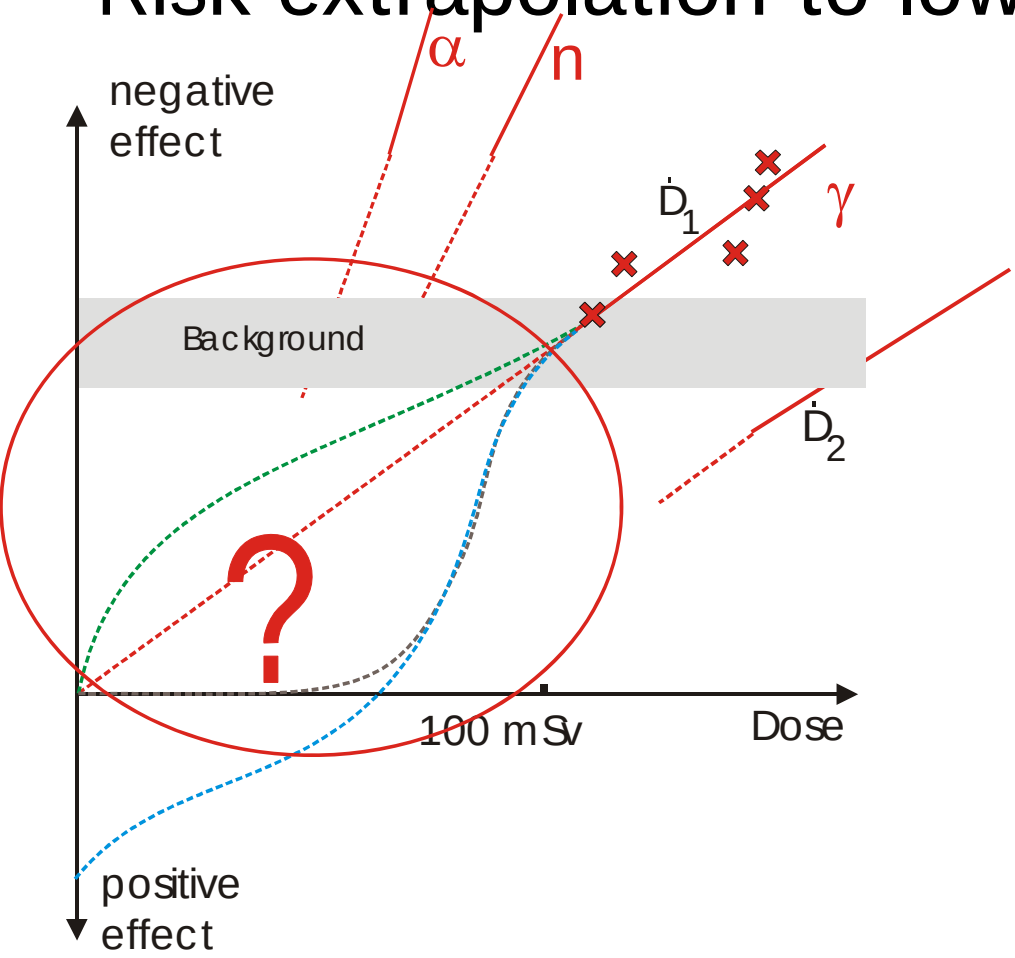
Alpha-risk :Nombre de partenaires 18, venant de 9 pays

Work-Package		WP Leadership
WP1	**Cohorts of uranium miners**	**IRSN (D. Laurier)**
WP2	**Indoor radon studies**	**CR-UK (S. Darby)**
WP3	**Nested case-control studies of lung cancer and leukaemia among nuclear industry workers**	**IARC (E. Cardis)**
WP4	**Cohorts of nuclear workers with internal exposure**	**WSC (K. Binks)**
WP5	**Organ dose**	**USALZ (W. Hofmann)**
WP6	**Integration of results**	**HPA(ex-NRPB) (C.Muirhead)**
WP7	**General management**	**IRSN (G. Monchaux)**

Forte puissance d'analyse, car suite logique de programmes déjà lancés durant le 4e et le 5e PCRD

6ème PCRD - biologie

Risk extrapolation to low + protracted doses



- Epidemiological studies have insufficient power to detect cancer risks at the low doses (say <50mSv).
- There is insufficient knowledge on common genetic factors that might determine inter-individual differences in low dose cancer risk.
- Rational judgments in radiation protection require extrapolation procedures to judge the effects of low doses and low dose-rates of radiation. Therefore, it is essential to have a detailed knowledge of the basic mechanisms by which radiation induces cancer.

European Project IP-FP6 RISC-RAD 2004-2008

RISC-RAD

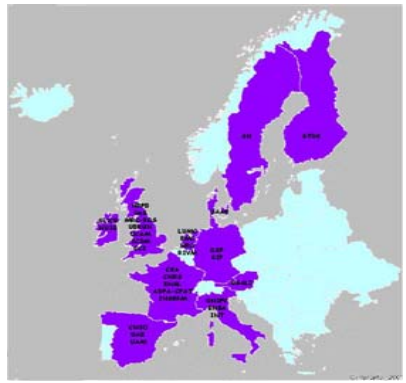
Radiosensitivity of **I**ndividuals and **S**usceptibility to **C**ancer induced by ionizing **RAD**iations

GENERAL INFORMATION

- **RESEARCH TOPIC :** **EURATOM / Radiation Protection**
- **INSTRUMENT :** **Integrated Project**
- **COORDINATION :** **CEA, Direction des Sciences du Vivant,**
- **COORDINATOR :** **Laure Sabatier**
- **DURATION :** **4 ans (2004-2008)**
- **CONSORTIUM :** **29** European institutes through 11 countries

  33 research teams, or a network of 380 persons
  (scientists, post-doc, PhD, undergraduates students, technical assistants, administrative…)

- **BUDGET :**
  - **Total :** **15-30 M€**
  - **Contribution U.E :** **10 M€**
  - **Part du CEA :** **1,694 M€**



EURATOM

European Project
IP-FP6
RISC-RAD
2004-2008

A
Low Doses Versus High Doses

B
Heritable Factors

C
Model For Cancer Risk

WP1 LM — INITIAL DNA DAMAGE BY IR
DNA REPAIR
CELL CYCLE RESPONSES APOPTOSIS

WP2 LS — EPIGENETIC CHANGES
CHROMOSOMAL INSTABILITY

WP3 SB — PRENEOPLASTIC LESIONS
AND TUMOUR DEVELOPMENT

WP4 MA — GENETIC SUSCEPTIBILITY
TO IR-INDUCED CANCER

WP5 HP — MODELLING RISK ASSESSMENT

WP7 Management activities

Management board

Project Board
Coordinator : L.Sabatier
Scientific Manager : L.Mullenders
WP Leaders Topical leaders

Secretary
Coordinator Assistant: G.Decroix
Scientific Assistant : B.van Zeeland
Financial Assistant : A.Grassin
Communication Assistant : A.Meunier

Scientific committee

Integration Steering Committee

Dissemination and Training activities

WP6 CEA

Task 1
Collaborative platform

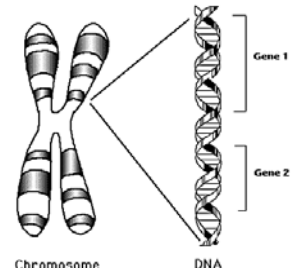
Task 2
Meeting and Training

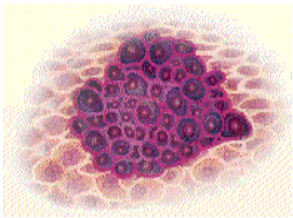
Task 3
Dissemination tools
Leaflet, web site, newsletter, etc

RISC-RAD

Radiosensitivity of **I**ndividuals and **S**usceptibility to **C**ancer induced by ionizing **RAD**iations

ORGANISATION OF RESEARCH : an integrated approach





- DNA DAMAGE
- DNA REPAIR
- CELL CYCLE RESPONSES
- APOPTOSIS
- GENOMIC INSTABILITY

WP 1 and 2

- PRECANCER LESIONS
- CANCER
- GENETIC SUSCEPTIBILITY TO CANCER
- IDENTIFICATION OF GENES

WP 3 and 4

from DNA DAMAGE

MODELLING AND RISK ASSESMENT

WP 5

to CANCER

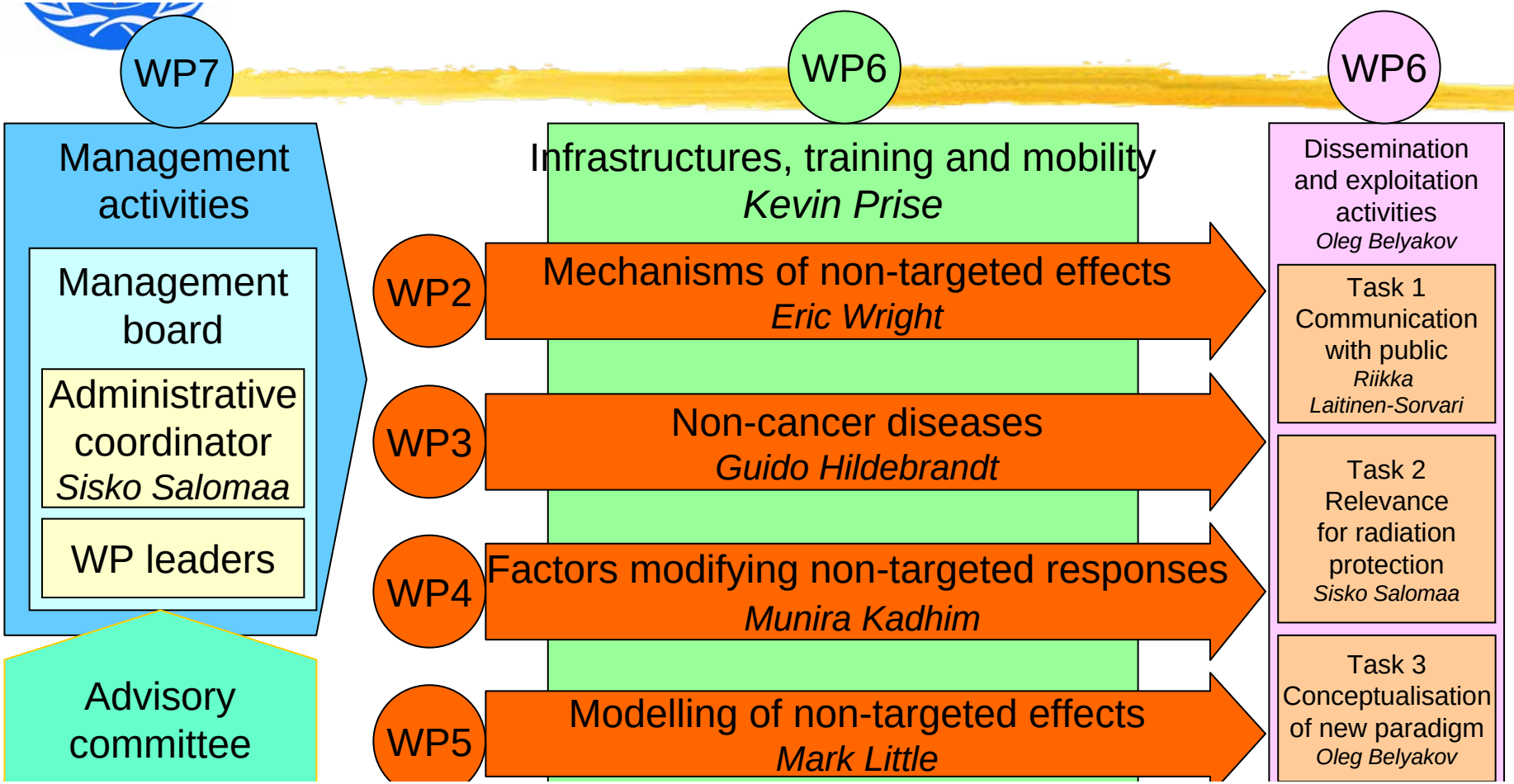
EURATOM

General information

- NOTE IP is in negotiation stage at the moment
- Duration: 48 months
- Tentative start date of the project: 1 September 2006
- 19 partner organisations
- Coordinating organisation: STUK - Radiation and Nuclear Safety Authority
- Project coordinator: Prof. Sisko Salomaa
- EURATOM Specific Programme for Research and Training on Nuclear Energy, 6th Framework Program
- Tentative budget: 11.89 M€

General objectives of the NOTE IP

- To investigate the mechanisms of non-targeted effects, in particular, bystander effects, genomic instability and adaptive response.
- To investigate if and how non-targeted effects modulate the cancer risk in the low dose region, and whether they relate to protective or harmful functions.
- To investigate if ionising radiation can cause non-cancer diseases or beneficial effects at low and intermediate doses.
- To investigate individual susceptibility and other factors modifying non-targeted responses.
- To assess the relevance of non-targeted effects for radiation protection and to set the scientific basis for a modern, more realistic, radiation safety system.
- To contribute to the conceptualisation of a new paradigm in radiation biology that would cover both the classical direct (DNA-targeted) and non-targeted (indirect) effects.


WP7
Management activities
Management board
Administrative coordinator
Sisko Salomaa
WP leaders
Advisory committee
WP6
Infrastructures, training and mobility
Kevin Prise
WP2
Mechanisms of non-targeted effects
Eric Wright
WP3
Non-cancer diseases
Guido Hildebrandt
WP4
Factors modifying non-targeted responses
Munira Kadhim
WP5
Modelling of non-targeted effects
Mark Little
WP6
Dissemination and exploitation activities
Oleg Belyakov
Task 1
Communication with public
Riikka Laitinen-Sorvari
Task 2
Relevance for radiation protection
Sisko Salomaa
Task 3
Conceptualisation of new paradigm
Oleg Belyakov

Priorités pour le 7ème PCRD - *Thèmes de recherche*

- Faibles doses – populations/expositions à étudier
  - Travailleurs
  - Expositions pédiatriques
    - Scanners CT
    - Cancer du sein après Tchernobyl
    - Faisabilité d'études d'autres expositions médicales (Prématurés, radiologie interventionnelle)

Priorités pour le 7ème PCRD - *Thèmes de recherche*

- Faibles doses
  - Différents types d'exposition et nouvelles technologies
    - Protonthérapie: mécanismes moléculaires et suivi épidemiologique
  - Facteurs de modification du risque – interaction gène/rayonnements
    - Cohortes de porteurs de mutations (BRCA1, BRCA2, ATM hétérozygotes)
    - Gene-Rad-Risk

Priorités pour le 7ème PCRD

- Nécessité d'une approche intégrée
  - Épidémiologie-biologie
  - Supranationale: « infrastructure virtuelle » européenne ?
    - Épidémiologie
      - ✓ Manque de puissance statistique au niveau national (depuis le 4ème PCRD déjà études concertées au niveau européen et international)
    - Biologie
      - ✓ Complémentarité et non duplication

... Objectifs des différents partenaires pas toujours compatibles

- Favoriser une réflexion et une planification communes
- Déjà en cours grâce au CT Euratom en France
- Faisabilité d'étendre l'approche à d'autres partenaires européens?